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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/712,028	11/13/2000	Paul H. Patterson	A-65182-1/RFT/JJD	9117

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EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/712,028	PATTERSON ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election of the invention of group I, claims 1-23 in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 24 and 25, drawn to non-elected invention, have been cancelled as requested by the applicants.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating inflammation, swelling associated with inflammation or infiltration of macrophages associated with inflammation at a cutaneous site, comprising the step: directly administering to the site an expression vector, wherein said expression vector comprises a nucleic acid encoding full length LIF and wherein said nucleic acid is operably linked to a promoter, wherein said promoter expresses the nucleic acid in the skin cells at the site and wherein the LIF is expressed in the skin cells at the site, does not reasonably provide enablement for any other embodiments of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed invention commensurate in scope with these claims.

Claimed method encompasses any route of administration, any site of inflammation and any nucleic acid encoding LIF. However, the specification as filed does not provide sufficient guidance to practice the claimed method commensurate with the full scope of the claims and an artisan of skill would have required

extensive experimentation to practice the claimed invention commensurate with the scope of claims and such experimentation will be undue since the art of gene therapy is unpredictable, the role of LIF in inflammation varies depending on the site of inflammation and the specification does not provide sufficient guidance to address these issues for an artisan to practice the claimed invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification has disclosed that LIF mRNA expression is increased at the site of injection of CFA by intraplantar injection. The specification also discloses that the increase in LIF mRNA was greater in a LIF knockout mice (see page 32). The specification further discloses that injection of LIF into rat hindpaw before induction of inflammation with CFA resulted in reduced inflammation (see page 34). The specification teaches an adenovirus vector that comprises LIF encoding nucleic acid sequence and that injection of the virus intradermally resulted in suppression of inflammation and macrophage cell infiltration (see pages 39 and 40). These

teachings indicate the anti-inflammatory effects of LIF in skin and that a vector when injected at the site of inflammation reduces inflammation.

However, these results do not indicate or provide evidence that when any nucleic acid encoding LIF is administered by any route to a patient or a subject, it would reduce inflammation, swelling associated with inflammation or infiltration of macrophages at any site. First, the art of record indicates that CFA has different effects on inflammation at different sites. For example, while in skin it has anti-inflammatory effects, it has a pro-inflammatory effect in nervous system. In fact, studies from inventors' groups reported that while LIF had an anti-inflammatory role in cutaneous inflammation (see Zhu et al. The Journal of Immunology 166:2049-2054, 2001; Banner et al. The Journal of Neuroscience 18:5456-5462, 1998), in the nervous system, LIF was pro-inflammatory (see Sugiura et al. European Journal of Neuroscience 12: 457-466, 2000). In page 464, second full paragraph in the right column, Sugiura et al noted: "These results are clearly opposite to those obtained in the present work, indicating that LIF can have very different actions in distinct locations and or with different types of inflammatory stimuli". Gadient and Patterson (Stem Cells 17:127-137, 1999) also discussed the difference between the effects and roles of LIF in neural inflammation and cutaneous inflammation (see table 1 on page 129 and pages130-131). Therefore, it is not clear as to how will an artisan use LIF in decreasing inflammation or other recited conditions by expressing LIF in nervous system or other locations other than in the skin. White applicants have used the term "modulating inflammation", which will include both an increase as well as decrease, the specification does not teach as to how to use increase in inflammation in treatment.

Next, the art of gene therapy is unpredictable. Numerous factors complicate the gene delivery art which would not have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the

stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used and the protein being produced. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. Deonarain (Deonarain MP. Exp. Opin. Ther. Patents. 8:53-69, 1998) also noted that gene delivery remains the major technological stumbling block in gene therapy strategies. Deonarain further noted that there are several drawbacks of different targeting vectors, such as, risk of secondary malignancies due to integrated vectors, recombination of disabled viruses to produce infective virus, lack of cell specificity, lack of infection of non-dividing cells by retrovirus, inactivation and inactivation of the viral vectors by host complement (see column 1 continued in column 2 on page 54). Romano et al (Romano et al. Stem Cells 2000; 18:19-39) reporting on the recent developments of gene therapy, noted,"However, the real effectiveness of gene therapy programs is still in question. After a decade of clinical trials, the therapeutic applications of gene transfer technology are still at a rather preliminary stage." It is noted that these reviews by the leaders in the field of gene therapy are about those gene therapy protocols and applications where the mechanism of action and some efficacy has been determined in animals models and there may be some extrapolatable correlations indicating the therapeutic effects of a particular gene's encoded protein. In the instant case, the specification does not teach as to how a nucleic acid encoding LIF will be directed to a site of inflammation in the body to another site and whether sufficient amount of LIF could be produced to modulate inflammation. Furthermore, the specification does not provide any guidance as to what doses of a nucleic acid will be administered to target a nucleic acid to a site other than the site of administration. While applicant's specification supports efficient transfer for *in vivo* direct injection into skin, the specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved by any mode of delivery. The specification

fails to teach any specific targeting techniques, fails to provide any working examples, which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art, which would allow one of skill in the art to practice the claimed invention without undue experimentation.

Therefore, limiting the scope of the claimed invention to a method of modulating inflammation, swelling associated with inflammation or infiltration of macrophages associated with inflammation at a cutaneous site, comprising the step: directly administering to the site an expression vector, wherein said expression vector comprises a nucleic acid encoding full length LIF and wherein said nucleic acid is operably linked to a promoter, wherein said promoter expresses the nucleic acid in the skin cells at the site and wherein the LIF is expressed in the skin cells at the site, is proper.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01.

The omitted elements are: wherein said nucleic acid is expressed and the LIF produced modulates inflammation. It is noted that the claim as instantly recited does not recite a step that relates back to the preamble.

7. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to **§** 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER